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ON THE CAUSE OF LIVER NECROSIS AFTER THE INTERRUPTION OF THE HEPATIC ARTERY IN DOGS

by

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INTRODUCTION

RIENHOFF, BERMANN and others advocated the ligation of hepatic and splenic arteries for the treatment of the portal hypertention, but this operation has been generally accepted to be dangerous because of liver necrosis following the ligation.

On the other hand, however, TSUCHIYA, in our clinic, produced a state with ascites similar to liver cirrhosis in dogs by the constriction of the hepatic vein under the diaphragm, and recognized that liver necrosis after the hepatic artery ligation in these dogs was hard to occur as compared with those having no ascites.

It is the main purpose of this report to investigate the mechanism of development of liver necrosis after the hepatic artery interruption in normal dogs, and to see the reason why liver necrosis is hardly to occur in ascitic dogs after the interruption

of the hepatic artery.

When three arteries (The Common Hepatic Artery, Gastroduodenal Artery and Right Gastric Artery) are simultaneously ligated and cut off in normal dogs, the arterial blood flow to the liver come to be almost interrupted and most of them die of massive liver necrosis.

MARKOWITZ, administrating penicillin, reduced the mortality rate after the hepatic artery ligation. From the results of TANTURI, FINE and others, it has been generally accepted that liver necrosis following the hepatic artery ligation is due to the proliferation of anaerobes normally present in the liver of dogs.

Observing the liver necrosis following the hepatic artery interruption in many dogs, and refering to the experimental results in our clinic, I have come to consider the process of liver necrosis following the interruption as follows:

1) Liver necrosis after the interruption develops massively and localizedly, and has its own favorite sites in the liver; that is, it develops in the lower peripheral parts of the caudate, quadrate, middle and left lobes and seldom in the right lobe.

2) URABE, in our clinic, administered a single dose of 100,000 units of penicillin immediately after the hepatic artery interruption and reduced markedly the mortality rate after the interruption. He also indicated that in spite of giving a greater dose of penicillin, he could not obtain the lowering of mortality rate anymore, and that 100,000 units of penicillin given intramuscularly immediately after the hepatic artery interruption maintained its antibiotic effects which was displayed in the liver within only 8 hours postoperatively.

3) YAMABE, in our clinic, proved the presence of lecithinase, α toxin of clostridium, in the areas of liver necrosis after the interruption, but it appeared only after 12 hours of the interruption. He also recognized that though lecithinase was demonstrated in the regions of necrosis after the interruption, it was not shown in the regions, where any abnormalities was not found macroscopically other than congestion, in one and the same liver.

Still more he ascertained the existence of anoxemic liver necrosis in which lecithinase was not proved.

These three points as mentioned above lead us to the following concepts: That is, even though anaerobes take part in liver necrosis following the interruption, it is at the last step to the liver necrosis, and there comes the former step on which the proliferation of anaerobes was founded.

This former step may be established within 12 hours after the interruption, and it is hardly considerable that the action of penicillin administered after the hepatic artery interruption is only on anaerobes themselves.

From this point of view, I came to consider that the changes of the liver in the course of 12 hours after the operation were especially closely related to the mechanism of development of liver necrosis which occurred after the hepatic artery interruption.

In this sense, I observed grossly the changes of the liver following the interruption, and also investigated the rise and fall of the serum ADS and liver ferritin

in the order of hours after the operation.

CHAPTER 1 SERUM ADS AFTER THE HEPATIC ARTERY INTERRUPTION

a) ADS (anti-diurctic substance)

Since GIBBUS announced the method of the measurement of the antidiuretic substance for the first time in 1930, ADS in serum and urine has been proved in various kinds of diseases and stresses according to the progress of the method of its measurement.

It is thought that the posterior pituitary hormone probably plays the important part in the serum ADS. But as the way of its measurement can'not but be depended upon the bioassay, it seems natural to take it that, as LLOYD says, the serum ADS represents the algebraic sum of all antidiuretic and diuretic substances contained in the serum.

The appearance of serum ADS after the hepatic artery interruption is first due to the surgical stress and secondary to ferritin mobilized from the liver after the interruption. The serum ADS originated from the former is considered, by SCHIBUZAWA, to be secreted by the way of hypothalamico-hypophysial system, and the antidiuretic action of ferritin is assumed, by BAEZ, MAZUR and SHORR, to be mediated through the neurohypophysis.

Therefore, it may be admitted that pitressin plays the most important role in the appearance of serum ADS after the hepatic artery interruption.

b) The Method of the Measurement

Various kinds of measurements were reported, but all of them were by the way of bioassay.

In my experiments, full grown male wistar strain rats, weighing about 120 g each, were used as assay animals. They were isolated in a quiet room and kept by only vegetables full of water at least for two days before being used and they were kept away from feeding on the experimental day.

At first I put Nelaton's Catheter No. 3 into their stomach, then infused 5 cc of water warmed to body temperature. The urine excreted was measured for 2 hours after the infusion in 30 rats.

The amount of urine excreted for 2 hours after the infusion was from 4.2 cc to 5.1 cc, 4.7 cc on an average (Fig. 1).

When pitressin by Parke, Davis Company was injected subcutaneously just after loading 5 cc of water, the extreme diminution of urine was recognized for 2 hours (Fig. 2).

In order to show numerically the rise and fall of the serum ADS after the hepatic artery interruption, I made the calculation to measure the antidiuretic activity of the serum.

Immediately after the infusion of 5 cc lukewarm water, I injected subcutaneously 1 cc of 5% glucose solution to the control rat and 1 cc of the serum to be examined to the assay rat under the same condition and measured respectively the amount of urine excreted for 2 hours after the injection. Setting each of them as A cc and B cc, I calculated the antidiuretic activity of serum as follows:

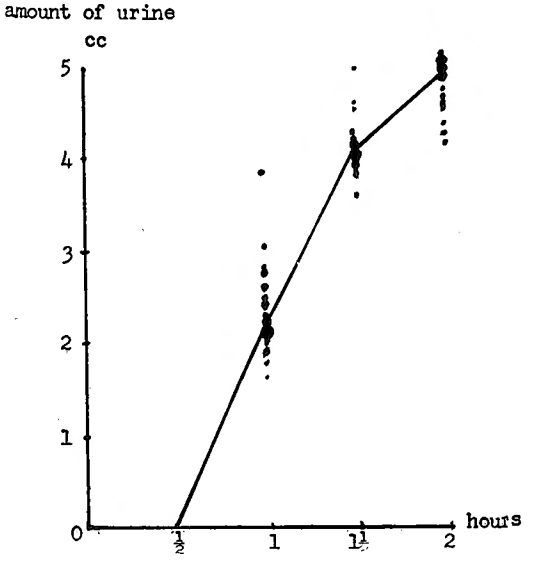


Fig. 1 Amount of urine excreted by loading 5 cc of water in rats

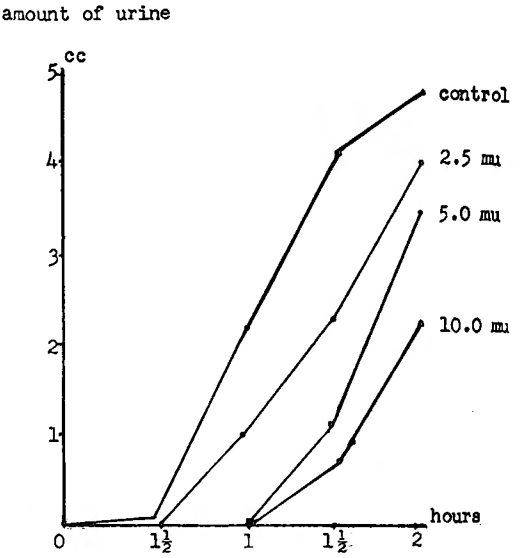


Fig. 2 Amount of urine excreted by loading 5 cc of water and injecting pitressin in rats

Table 1 ADS Measurement

control rat	loading 5 cc of lukewarm water	subcutaneous injection 1 cc of 5% glucose solution	amount of urine excreted for 2 hours after loading : acc
Assay rat	ditto	subcutaneous injection 1 cc of serum	ditto : bcc

Antidiuretic Activity of the Serum

$$ADA = \frac{a-b}{a} \times 100$$

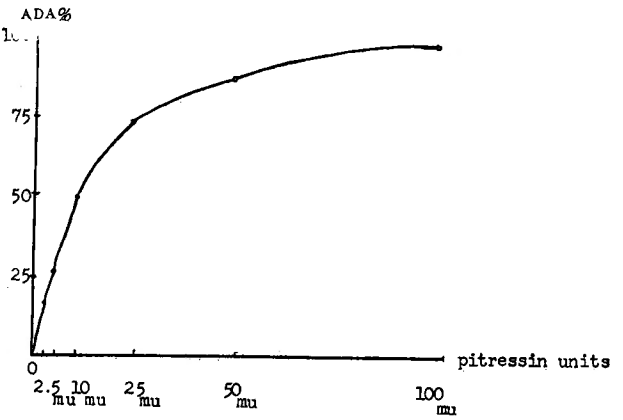


Fig. 3 Relationship between antidiuretic activity and pitressin unit

$\frac{A-B}{A} \times 100$ (Table 1)

I recongnized that the antidiuretic activity thus expressed had the mutual relationship with pitressin unit within from 2.5 milli units to 25 milli units of pitressin (Fig. 3).

It seemed that this method was good enough to know the rise and fall of serum ADS after the hepatic artery interrution. But this method does not fit for measurement in the high temperature and in the dry season like summer.

c) Results

Under the narcosis by ether, I performed the laparotomy, offering almost the same degree of operative manipulation as the interruption of three arteries (the common hepatic artery, right gastric artery and gastroduodenal artery) without actually interrupting them, and measured the serum ADS before and after the operation.

The value of serum ADS rises rapidly in 3 hours, falls in 6 hours, returning to the initial level in 12 hours after the operation.

But under the intravenous anesthesia used 0.5 cc per kg in body weight of nembutal by Abbot Company, any rise of the serum ADS is not seen in the same operative procedure as mentioned above; that is, by the use of nembutal the rise of the value of serum ADS is not induced by almost the same degree of surgical handling as interruption of the hepatic artery (Fig. 4).

I employed, therefore, this narcosis in order to know the rise and fall of serum ADS directly related to the change of the liver itself after the interruption of the hepatic artery.

The values of serum ADS after the interruption of the three arteries under

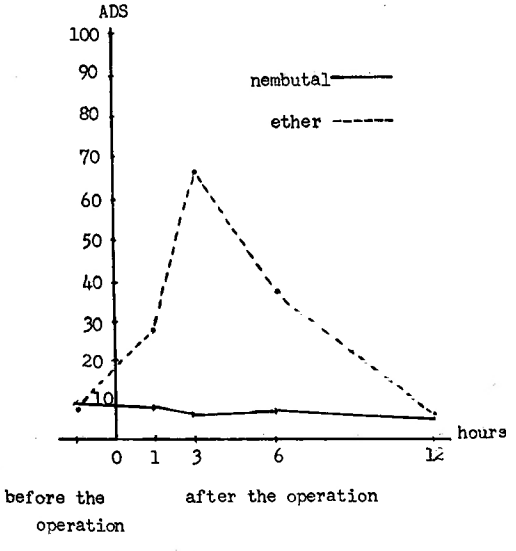


Fig. 4 Serum ADS before and after the probe laparotomy under anesthesia by ether and nembutal

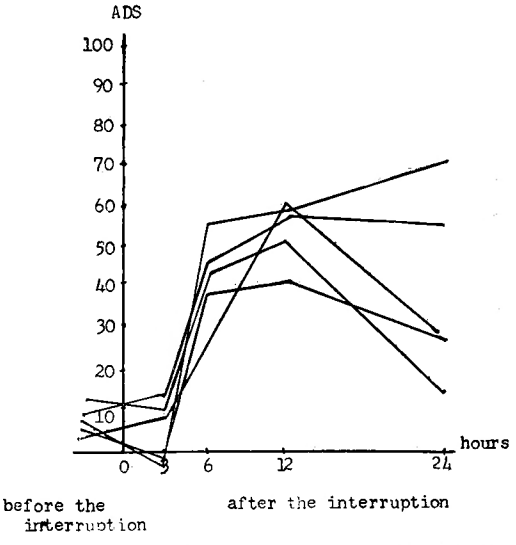


Fig. 5 Serum ADS before and after the hepatic artery interruption under the intravenous anesthesia with nembutal 0.5cc/kg

the intravenous nembutal anesthesia of 0.5 cc per kg in body weight are shown in Fig. 5.

Thus it may be assumed that these fluctuations of the value of ADS in serum are related closely to the morbid states of the liver after interruption of the hepatic artery including the mobilisation of liver ferritin into the blood stream and the deterioration of liver function to inactivate serum ADS.

The rise of the value of serum ADS gradually begins from about 3 hours after the operation and reaches its highest point from 6 hours to 12 hours after the interruption suggesting that the process to liver necrosis is carried on most markedly from 3 hours to 12 hours after the operation.

CHAPTER 2 MACROSCOPIC FINDINGS OF THE LIVER AFTER THE HEPATIC ARTERY INTERRUPTION

Although there are some differences in degree according to the individuality and the location of the liver, it generally brings about the changes in colors such as dark red or indigo blue over the whole liver immediately after the interruption.

MIYAWAKI, in our clinic, performed the roentgenological studies as follows: He infused urographin into the portal vein before and after the interruption. Before the interruption the flowing-out of urographin from the liver was very rapid, but it became gradually slow immediately after the interruption. In 3 hours after the interruption there still remained urographin locally in the liver 20 minutes after the infusion.

ISHIGURO, in our clinic, performed the pathohistological studies of the liver after the interruption and found the stasis of the intrahepatic portal blood flow.

So it can be thought that the changes in colors of the liver following the interruption are due to the stasis in the intrahepatic portal blood flow.

There were such cases in which the strong changes of colors into dark red were seen over the whole liver immediately after the hepatic artery interruption, and in them, 26 hours later, these changes were found to be extinguished except the localized congestive areas.

I believe that the stasis in the intrahepatic portal blood flow which can be seen after the hepatic artery interruption is reversible in nature and has the possibility to fade away so far as no other intrinsic factors are added.

When I observed grossly the liver changes following the interrption in the order of hours, this stasis which occurred all over the liver immediately after the interruption, gradually began to show the tendency to be localized at the 3rd postoperative hour, and it became distinctly localized in 12 hours.

The areas in which the localized congestion develop are situated, in the great number of cases, at the left, middle, quadrate and caudate lobes, all of which coincide with the favorite sites of liver nocrosis after the interruption.

MIYAWAKI found that liver necrosis developed afterwards in the regions where urographin infused into the portal vein remained locally.

As above mentioned, I considered, from the results of serum ADS, that the process to liver necrosis following the interruption began to set in at the 3rd

postoperative hour, and now also found that the localized congestion, which was considered macroscopically to be the first step to liver necrosis, gradually began at almost the same hour after the operation.

CHAPTER 3 HEPATIC FERRITIN AFTER THE HEPATIC ARTERY INTERRUPTION

a) Ferritin

Under the consideration that liver ferritin might have any relationship with the morbid state of the liver following the hepatic artery interruption, I investigated the liver ferritin.

Ferritin was discovered as protein including 7% iron by SCHMIEDEBERG in 1894, and then by LAUFBERGER it was obtained as a pure crystal including 19% iron in 1937. Ferritin exists mostly in the liver and plays an inportant part on the iron metabolism.

Recently SHORR and others reported that VDM appeared in the terminal blood of the experimental animals put in a state of shock. Then, they attributed the cause of irreversible shock to ferritin, identifing this substance with VDM.

According to them, ferritin decreases the vasomotion of the metaarterioles and precapillaries and dilates the precapillary sphincters, and thus brings about the congestion in the capillary bed.

SHORR demonstrated that although ferritin was destructed in the nomal liver, it could not merely be destroyed but its production in the liver was accelerated when the oxygen supply to the liver was reduced.

b) The Method of the Measurement

Ferritin fraction of the liver was prepared by YONEYAMA-KONNO's method, that is, I added 5 cc physiological saline solution to a piece of liver tissue weighing 1.0 g and homogenized, then took out the soluble part S_1 after warming for ten minutes at 80°C. Furthermore, S_1 was heated for thirty minutes at 100°C, then P_2, the part which was coagulated, was taken out by centrifugation. P_2 is the ferritin fraction. Extraction of iron from P_2 was done by ZONDEK's method. Iron was colored by o-phenanthroline and measured by BECKMANN's spectrophotometer.

c) Results

The diminution of liver ferritin after the hepatic artery interruption was already reported by KOSHIZUKA and MURATA in Japan.

Assuming that ferritin might have related to the development of localized congestion after the interruption, I measured hepatic ferritin contained in the normal area and also that in the congestive area after discriminating between these two areas by gross observation. In 3, 6, 12 and 24 hours respectively after the interruption, I took out a piece of the liver weighing about 3 g from the region thought to be normal and from the region where congestion with or without necrosis was presented, and measured the value of liver ferritin, then calculated the rate of diminution of ferritin comparing with that before the operation.

The results are shown in Table 2, and Fig. 6.

The diminution of liver ferritin in normal regions after the interruption was extremely slight, but in the regions where congestion or necrosis was demonstrated,

Table 2 Liver ferritin before and after the hepatic artery interruption

	cases	ferritin before interruption r/g	ferritin in normal regions r/g	ferritin in morbid regions r/g	rate of diminution in normal regions %	rate of diminution in morbid regions %	rate of diminution in normal regions (on an average %)	rate of diminution in morbid regions (on an average %)
3 hours after the interruption	1	137	135	136	1	0	1	6
	2	220	218	194	1	12		
6 hours after	1	340	320	240	6	29	5	31.5
	2	182	175	120	4	34		
12 hours after	1	322	285	74	11	77	7.5	70
	2	164	157	61	4	63		
24 hours after	1	97	84	30	13	69	10.5	74.5
	2	218	200	44	8	80		

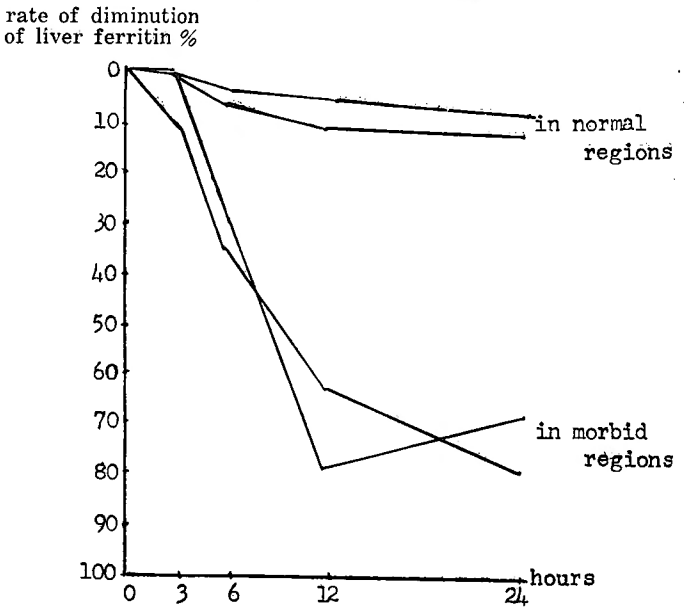


Fig. 6 Liver ferritin after the hepatic artery interruption

liver ferritin diminished remarkably from 3 hours to 12 hours after the interruption and not so marked after 12 hours.

It can be recognized that there is a relationship between the dropping curve of liver ferritin and the rising curve of serum ADS after the hepatic artery interruption, and that ferritin mobilized from congestive areas brings about the increase of serum ADS through the neurohypophysis (Fig. 7).

CHAPTER 4 LIVER FERRITIN AND SERUM ADS AFTER THE HEPATIC ARTERY INTERRUPTION UNDER THE ADMINISTRATION OF 100,000 UNITS OF PENICILLIN

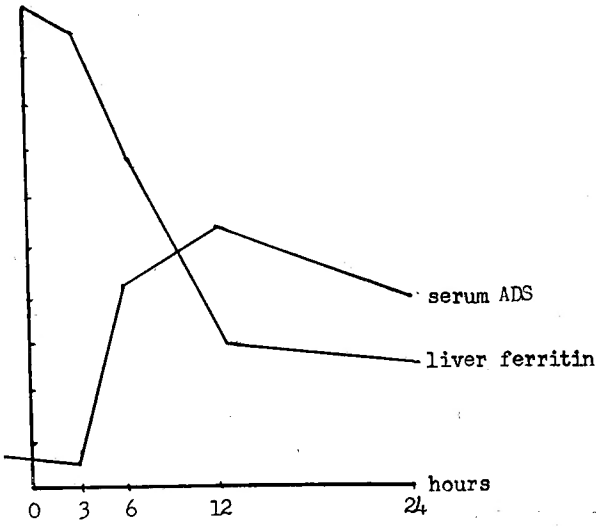


Fig 7 Serum ADS and liver ferritin after the hepatic artery interruption

a) Serum ADS

I cut off the three major arteries previously mentioned under double ligation and administered intraperitoneally 100,000 units of penicillin immediately after the operation.

In gross observations on two cases at the 26th hour after the operation, the morbid areas of the liver were extremely narrow in both cases and these cases seemed to be the ones that probably might have survived. The increase of serum ADS after the operation was hardly recognized (Fig. 8).

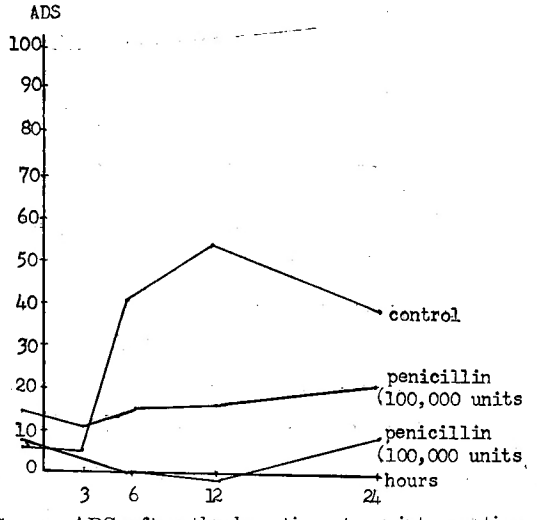


Fig. 8 Serum ADS after the hepatic artery interruption with the use of 100,000 units of penicillin

b) Ferritin

As shown in Table 3, and Fig. 9, even in the congestive areas the diminution

Table 3 Liver ferritin in morbid regions after the hepatic artery interruption with the use of 100,000 units of penicillin.

ferritin before interruption r/g	3 hours after the interruption		6 hours after		12 hours after		24 hours after	
	liver ferritin r/g	rate of diminuton %	l. f r/g	r. d. %	l. f r/g	r. d. %	l. f r/g	r. d. %
319			329	−3				
112					61	45.6		
238							113	52.6
180			158	12	94	48	85	53
186	184	1	178	4				
average at rate of diminution %		1		4.3		46.8		52.8

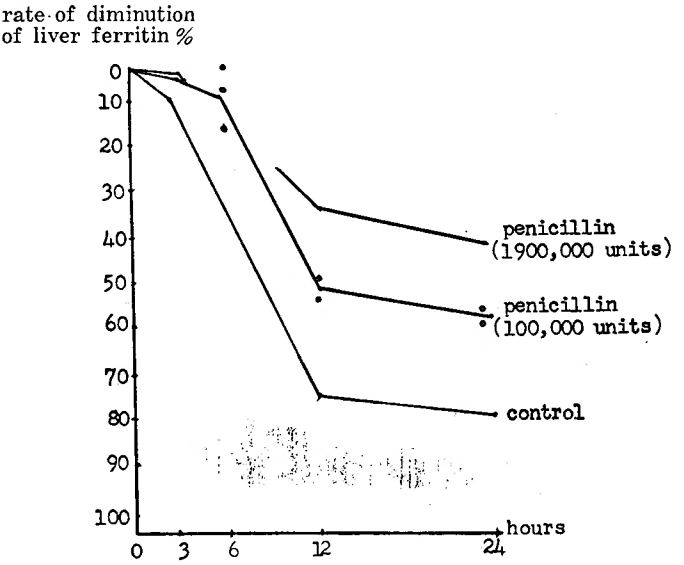


Fig. 9 Liver ferritin in morbid regions after the hepatic artery interruption under the administration of penicillin

of liver ferritin was not recognized till 6 hours after the operation.

Although the diminution of liver ferritin in the case, in which high units of penicillin were administered, found to be some what in a lower degree than that in which 100,000 units of penicillin was administered, yet it was observed after the 6th postoperative hour.

The reason why the increase of serum ADS is not recognized, dispite of diminution of liver ferritin, after the hepatic artery interruption under the administration of 100,000 units of penicillin, might be explained by the fact that the morbid area in which ferritin diminishes is so small that the amount of ferritin mobilized from the liver is of little significance.

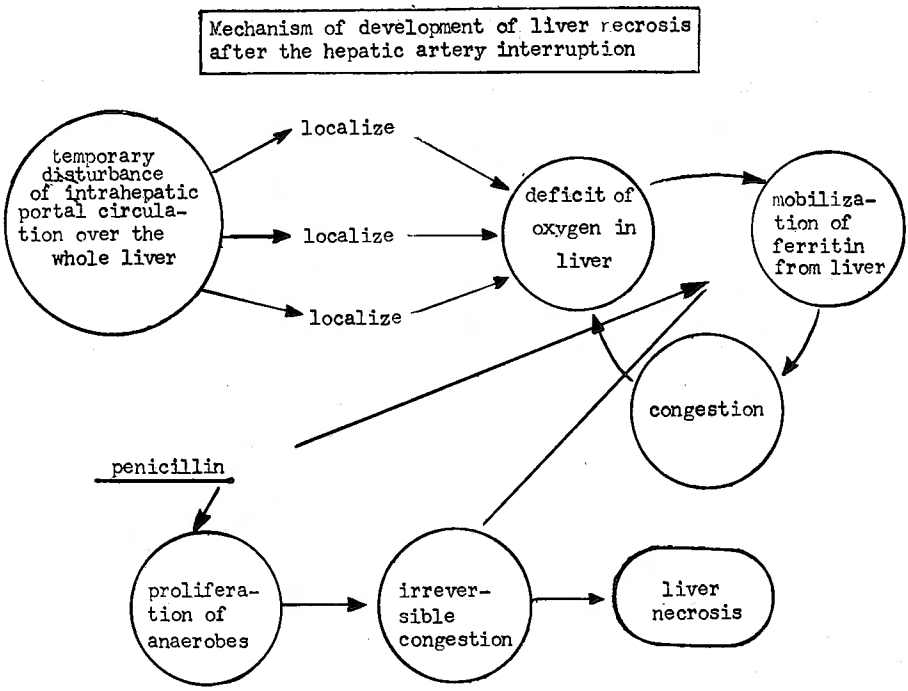
CHAPTER 5 THE MECHANISM OF DEVELOPMENT OF LIVER NECROSIS AFTER THE HEPATIC ARTERY INTERRUPTION

By the gross observation of the liver after the interruption of the hepatic artery, it was found that the localized irreversible congestion began to proceed gradually at the 3rd postoperative hour, and this localized congestion is believed to give rise to the development of liver necrosis.

In these congestive areas liver ferritin was found to be diminished, while in the normal areas its diminution was hardly recognized. On the other hand, the increase of serum ADS was observed simultaneously with the diminution of liver ferritin.

From these facts I deduced on the mechanism of the development of liver necrosis which developed after the interruption of the hepatic artery in dogs as follows, as shown in Fig. 10.

Fig. 10



Changes in clors which are observed diffusely all over the liver after the interruption are due to the stasis in the intrahepatic portal flow. According to the location of the affected part in the liver, the recovery of this stasis does not occur evenly and there remain some areas where the recovery is retarded, and these areas doomed to liver necrosis.

Since the deficiency of oxygen is comparatively marked in the areas where the stasis remains more than 3 hours after the interruption, the mobilization of liver ferritin from these areas comes into play.

When once the mobilization of liver ferritin set in, the stasis can no longer be

restored and is rendered irreversible by ferritin which depresses the vasomotion.

Thus, a series of these phenomena - congestion, oxygen deficiency and mobilization of liver ferritin - constitutes the "circulus viciosus" and continues to circulate till 12 hours after the operation.

This maligne circulation causes the remarkable deficiency of oxygen in the localized congestive areas, leading to the proliferation of anaerobes in these areas about 12 hours after the operation, and to the development of wet liver necrosis.

In other words, I have come to the conclusion that this localized, irreversible congestion presented the basis on which liver necrosis developed, and that liver ferritin participated in this process.

It was demonstrated that penicillin which had been administered immediately after the interruption restricted the mobilization of liver ferritin from the liver within 6 hours after the operation.

It is assumed that penicillin prevents the reversible stasis from going into the irreversible one which is the last step to liver necrosis, with the result of making a reduction in the extent of the irreversible stasis.

According to VOGEL and others, antibiotics such as penicillin reduce the oxygen consumption in the normal and hyperthyroid rats lowering their metabolic activity.

It is, therefore, admitted that penicillin would restrict the mobilization of liver ferritin which is caused by the deficiency of oxygen in the liver after the interruption of the hepatic artery.

CHAPTER 6 CASES OF THE HEPATIC ARTERY INTERRUPTION WITH THE USE OF ATROPIN, ACETYLCHOLIN AND DIBENAMINE RESPECTIVELY, AND CASES WITH ASCITES PRODUCED BY CONSTRICTION OF THE INFERIOR VENA CAVA ABOVE THE DIAPHRAGM

The development of liver necrosis following the hepatic artery interruption being due to the process stated above, it comes to my idea that dogs must be kept alive after the operation by checking the process to liver necrosis at its first step even under no administration of antibiotics. In other words, if the development of the localized, irreversible congestion which is the basis of proliferation of anaerobes is to be prevented, if the acute stasis in the intrahepatic portal flow is haemodynamically stoped, if the mobilization of liver ferritin is restricted, or if the specific action of ferritin on blood vessels is checked, the dogs are expected to survive the operation under no administration of penicillin.

URABE succeeded in reducing the mortality rate of dogs after the interruption of arterial flow to the liver by releasing the blood flow intermittently prior to the permanent interruption without using any antibiotics.

I am going to report here that I could prevent liver necrosis in considerable number of cases after the hepatic artery interruption with the use of atropin, acetylcholin and dibenamine.

a) Cases with the Use of Atropin

With the use of 0.5 mg per cc atropin sulfate, amounting from 6 cc to 11 cc,

Table 4 Cases with the administration of atropin

cases	body weight kg	sex	hours of administration after the interruption	total doses of 0.5 mg/cc atropin sulfate cc	
1	6.0	♂	6	6	survive
2	6.0	♂	10	6	survive
3	7.0	♂	10	6	survive
4	6.0	♂	10	6	survire
5	7.0	♂	4	8	dead (on the third postoperative day)
6	9.0	♂	5	9	dead (on the fourth postoperative day)
7	8.3	♂	4	9	survive
8	7.0	♀	5	11	survive
9	8.6	♀	4	9	dead (on the second postoperative day)

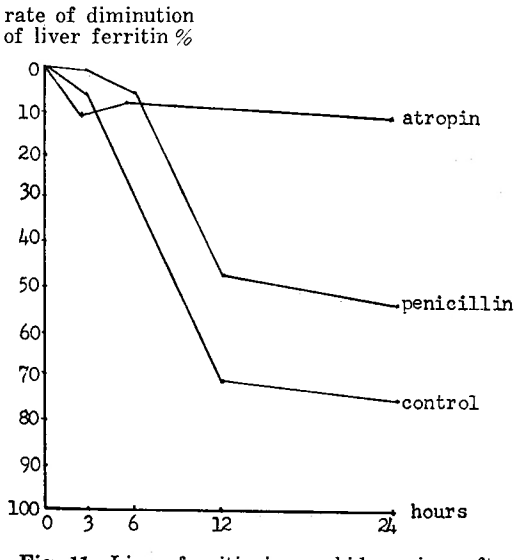


Fig. 11 Liver ferritin in morbid region after the hepatic artery interruption with the use of atropin

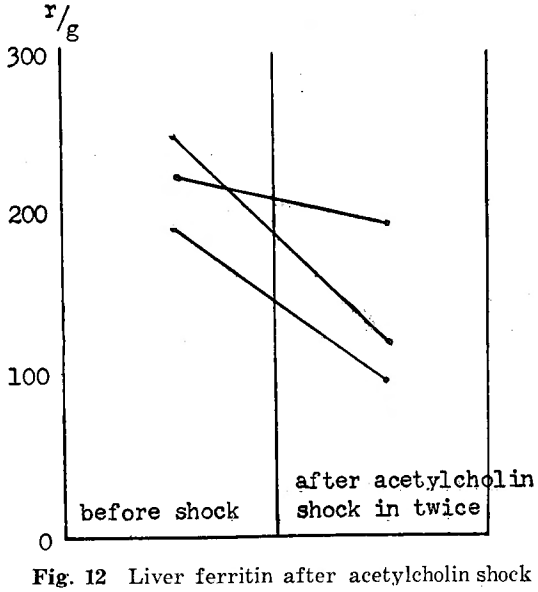


Fig. 12 Liver ferritin after acetylcholin shock

for 4 or 10 hours after the interruption, six dogs out of 9 examined could survive the operation (Table 4).

The diminution of liver ferritin after the interruption under the use of atropin was very slight (Fig. 11).

ADACHI, in our clinic, has proved the increase of oxygen content in the portal blood by atropin after the interruption.

It seems that the localized congestion which leads to liver necrosis did not happen to occur, because the mobilization of liver ferritin was restricted by the use of atropin.

b) Cases with the Use of both Atropin and Acetylcholin

On the day before the interruption and again 3 hours before the operation, I injected 0.1 g acetylcholin in 5 cc distilled water into the femoral vein causing the acetylcholin shock in dogs in two times. After that I performed the hepatic artery interruption and used from 6 cc to 10 cc of atropin for about 5 hours after the interruption.

All of the four experimental dogs could survive the operation (Table 5).

Table 5 Cases with the use of both acetylcholin and atropin

cases	body weight kg	sex	acetylcholin 0.1 g	atropin sulfate 0.5 mg/cc: hours of administration after the operation	atropin sulfate 0.5 mg/cc: total doses cc	
1	8.5	♂	on the day before the operation and on the operation day intravenous injection once a day	6	10	survive
2	8.4	♂	〃	4	6	surviue
3	10.0	♂	〃	4	6	survive
4	10.0	♂	〃	5	8	survive

The remarkable diminution of liver ferritin after the acetylcholin shock has already been reported by MURATA in Japan, and I also got the same result as shown in Fig. 12.

The diminution of liver ferritin in liver cirrhosis has also been reported by many investigators, and, from this point of view, it may be admitted that the interruption of the hepatic artery in the cirrhotic liver is comparatively safer than in normal dogs.

c) Cases with the Use of Dibenamine

I injected intramuscularly 10 mg or 20 mg of dibenamine one hour each before and after the interruption.

Three cases out of five were able to survive the hepatic artery interruption.

The effect of dibenamine in haemorrhagic shock is shown in Fig. 13 quoted from BAEZ's. BAEZ also stated the specific action of dibenamine on the liver ferritin system, and remarked that this action was rather enfeebled by the use of its large doses. In my experiment, all of the cases in which 20 mg of dibenamine was used died after the interruption. The cause of death may be attributed to the fact stated above.

d) Cases with Ascites produced by Constriction of the Inferior Vena Cava above the Diaphragm

In these ascitic dogs, the development of liver necrosis after the interruption was not found.

Liver ferritin was found to be remarkably diminished in them (Fig. 14), and also its diminution after the interruption was hardly be recognized (Fig. 15).

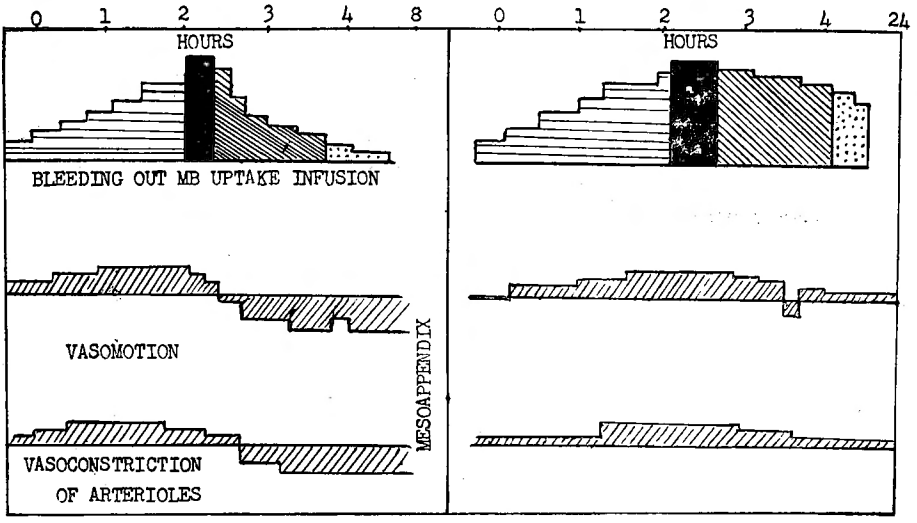


Fig. 13

Hemorrhagic shok in normal rat — Hemorrhagic shok in rat pretreated with dibenzyline (688-A)

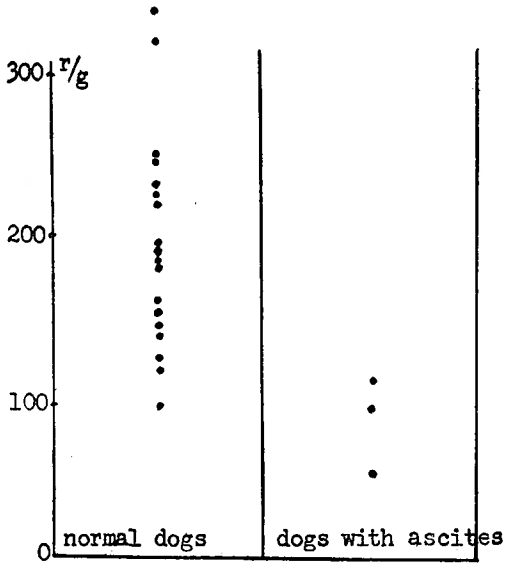


Fig. 14 Liver ferritin in dogs with ascites in which the constriction of inferior vena cava above the diaphragm was done

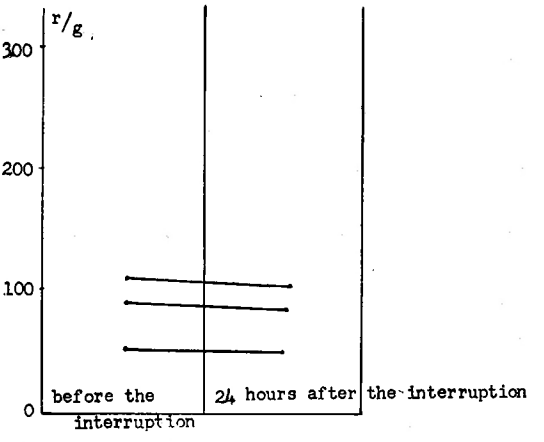


Fig. 15 Liver ferritin in morbid regions after the hepatic artery interruption in ascitic dogs

These findings of ascite dogs, speaking from the standpoint of ferritin, were quite the same with those of normal dogs in which both acetylcholin and atropin were used.

Considering from the fact that the livers of ascitic dogs haemodynamically have much similarity to those of cirrhosis in men, it may be admitted that the interrup-

Table 6 Cases with the use of dibenamine

Cases	body weight kg	sex	doses of dibenamine 10 mg/cc		
1	11.6	♂	at 1 hour each before and after the operation	1 cc	survive
2	10.0	♂	〃	1 cc	survive
3	11.5	♀	〃	1 cc	survive
4	8.5	♀	〃	2 cc	dead(48 hours after the operation)
5	10.0	♀	〃	2 cc	dead(24 hours after the operation)

tion of the hepatic artery could be carried out without danger in the case of liver cirrhosis.

CHAPTER 7 SUMMARY AND DISCUSSION

Concerning the mechanism of the development of liver necrosis after the interruption of the arterial blood flow to the liver, I have come to have an idea that the stasis in the intrahepatic portal flow which arise haemodynamically after the interruption and the disturbance of ferritin metabolism induced by the lack of oxygen locally shown in the hepatic tissue are put into action one after another constituting the circulus viciosus, and at last, the localized irreversible congestion on which anaerobes are able to multiply is formed leading to mushy liver necrosis.

The reason why liver necrosis after the hepatic artery interruption is not seen in liver cirrhosis with ascites has to be explained by the process before anaerobes are concerned.

According to Hosono's experiment, in our clinic, when the arterial blood flow to the liver is interrupted in normal dogs, the amount of the portal blood flow increases rapidly for a short time after the interruption and then tends to decrease continuously becoming smaller than that before interruption, which in ascitic dogs, it does not show any decrease but rather an increase.

If the diminution of the portal blood flow after the interruption means the stasis of the blood in the intrahepatic portal system, it seems that this stasis does not come into play in ascitic dogs. Regardless whether this is due to the existence of abundant collateral blood flow in the portal system, or not, it may be said that the stasis in the intrahepatic portal system following the interruption is haemodynamically difficult to occur in these cirrhotic livers accompanied by ascites.

As the factor which leads this stasis to irreversible congestion, I picked up ferritin. The content of this ferritin in the cirrhotic liver is found to be smaller than that in normal ones.

Adachi of our clinic has already shown that after the hepatic artery interruption in ascitic dogs, whose inferior vena cava has previously been constricted above the diaphragm, the content of oxygen in the portal blood showed an increase. Therefore, the degree of oxygen deficit in the cirrhotic liver after the interruption of the hepatic artery is slight, and accordingly, the mobilization of liver ferritin can be restricted.

After all, as far as ferritin is concerned, the cases of liver cirrhosis accompanied

by ascites correspond well to the cases in which both acetylcholin and atropin are administered.

It is justfiably admitted that in the case of liver cirrhosis with ascites liver necrosis can hardly be developed after the interruption of the arterial blood flow to the liver, because of the absence of the stasis in the portal system or of the mobilization of liver ferritin.

CHAPTER 8 CONCLUSION

1) On the basis of my experimental result, I have tried to inquire into the mechanism of the development of liver necrosis after the interruption of arterial blood flow to the liver, refering to a great deal of experimental results in our clinic.

It is assumed that the localized irreversible congestion which begin to appear gradually in the liver about 3 hours after the interruption of the hepatic artery is destined to become the basis of the development of necrosis, on which anaerobes have a chance to proliferate.

2) It is proved that liver ferritin is closely related to the development of this localized irreversible congestion giving an explanation of the effectiveness of penicillin.

That is, by an injection of 100,000 units of penicillin, the mobilization of liver ferritin from the liver is restricted for 6 hours after the interruption of the hepatic artery. That is the reason why the administration of a single dose of one hundred thousand units of penicillin could reduce the mortality rate after the hepatic artery interruption in normal dogs.

3) In order to restrict the mobilization of ferritin from the liver, or to check the specific action of ferritin after its mobilization, atropin, dibenamine, or both atropin and acetylcholin were used before and after the occulsion of the hepatic artery. By the aid of these drugs, I could prevent liver necrosis in considerable number of cases without using any antibiotics.

4) Together with the fact that the disturbance of the intrahepatic portal circulation due to the hepatic artery interruption is difficult to occur, the lowering of ferritin content in ascitic dogs lead us to expect that the interruption of the arterial flow to the liver in ascitic dogs is to be tried with safety.

In closing my report, I would like to express my deep appreciation to Prof. Dr. CHISATO ARAKI for his guidance and to Assistant Prof. ICHIO HONJO for his zestiful encouragement and guidance throughout my work.

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和文抄録

肝動脈血流遮断による肝壊死発生機序について

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肝硬変症治療の一環として最近 Rienhoff 及び Bermann 等が肝動脈結紮を提唱したが，この術式は肝壊死発生の危懼の故に一般に危険視されて来た．

正常犬で肝動脈を遮断すれば広範な肝壊死の発生を見るが，腹水の貯溜せる肝硬変類似の犬では遮断による肝壊死の発生し難いことが既に知られている．

肝動脈血流遮断による肝壊死発生機序を究明し，腹水の貯溜せる肝硬変症に於て壊死の発生し難い理由を知り，従来漠然と恐れられている肝動脈遮断後の肝壊死について何等かの解明を得たいと云うのが本実験の目的とするところである．

第1章　肝動脈血流遮断後の肝変化の肉眼的観察，血清 ADS 及び肝フェリチンの消長

正常犬で肝動脈血流を遮断すれば，一般に直後より肝全般に亘る暗赤色乃至藍色の色調の変化を見るがこれは肝内門脈系血行の鬱滞に起因するものである．この色調の変化は術後3時間過ぎより次第に限局性の傾向を示し12時間にて明らかに限局性となる．この限局性鬱血は遮断による肝壊死の好発部位に一致して発現する．

一方肝動脈遮断の手術侵襲そのものによる血清 ADS 上昇を除外し得たと考えられる測定法により遮断後の血清 ADS を測定するに，術後3時間過ぎより上昇し初め12時間にて最高となる．

肝フェリチンは遮断後肉眼的に鬱血部では3時間過ぎより急速に減少し初め6，12時間に亘り著明に減少する．肉眼的に遮断後なお正常と思われる部では肝フェリチンの減少は極めて少ない．

第2章　ペニシリン使用時肝動脈血流遮断後血清 ADS 及び肝フェリチン

遮断直後ペニシリン10万単位を腹腔内に投与し術後の血清ADS及び肝フェリチンを測定するに，血清ADSの上昇は殆ど認められず肝フェリチンは鬱血部にても術後6時間までその減少が抑制される．6時間以後，鬱血部にて肝フェリチンは減少するが一方血清 ADS 上昇の認められないのは，肝フェリチンの遊離せる肝鬱血部の範囲が極めて狭く血中に移行するフェリチンが少ないためと考えられる．

第3章　肝動脈血流遮断による肝壊死発生機序について

肝動脈を遮断すれば肝内門脈系血行の鬱滞を招来する．この血行障害自体は可逆性のものであり消褪し去るべき性質のものであるが，その消褪が遅れ術後3時間なお局所性に残存する部では比較的に酸素欠乏が強くフェリチンの遊離をみるに至る．このフェリチンは血管運動低下性に働き従つて鬱血は最早や消褪し得ず所謂不可逆性になると考えられる．

この鬱血，肝酸素欠乏，フェリチンの遊離が術後3時間過ぎより12時間に亘り一連の悪循環をなし限局性非可逆性鬱血を成立せしめると考えられる．

遮断による肝壊死への最終段階では嫌気性菌の関与するものであろうが，壊死部に於てレシチナーゼの証明されるのは遮断後12時間以後に於てであり，従つて限局性非可逆性鬱血が嫌気性菌増殖の基盤として，即ち遮断による肝壊死への前段階として特に重要であると考えられる．

ペニシリンは術後6時間までフェリチンの遊離を抑制し最初の可逆性の門脈血行障害が非可逆性鬱血へ移行するのを遅延せしめ最初の血行障害が回復するための時間的余裕を与える様に働くと考えられる．

遮断直後投与せるペニシリン10万単位の肝内有効時間は約8時間であるが，かゝる短時間しか効果がない

と思われるわずか10万単位のペニシリンが何故に遮断による肝壊死を防止し得るかと云う疑点もかゝる観点よりして説明し得るものと思う.

第4章 アトロピン，アセチールコリン，ダイベナミン使用に於ける肝動脈血流断例

上述よりすれば，肝壊死の前段階たる限局性非可逆性鬱血の発現を阻止すれば何等の抗生物質を用いずとも肝動脈遮断による肝壊死を防止し得るはずである.

i）アトロピン使用例

アトロピン 0.5mg/ccを遮断直後より4乃至10時間に亘り総計6乃至11cc使用し9例中6例の生存を見た. 遮断後の肝フェリチンの減少は極めて軽度であつた.

ii）アセチールコリン，アトロピン併用例

術前日及び当日アセチールコリン0.1gを静注しアセチールコリンショックを起こし先ず肝フェリチンを減少せしめしかる後肝動脈を遮断し術後アトロピンを併用した. 4例にて全例生存せしめ得た.

iii）ダイベナミン使用例

遮断前後各1時間にダイベナミン10mg乃至20mg筋注し5例中3例生存せしめ得た.

第5章 下空静脈狭窄による腹水貯溜犬の肝動脈血流遮断例

かゝる腹水貯溜犬では遮断による肝壊死発生を見ないが，遮断前より肝フェリチンは著明に減少しており又遮断後の肝フェリチン減少は極めて少ない. 肝フェリチンのみの立場からすれば正常犬でアトロピン，アセチールコリン併用例に相当する.

腹水を貯溜せる肝硬変症にては肝動脈遮断による肝内門脈系の血行障害が起り難いと考えられると共に，肝フェリチンが著明に少なく又遮断後の減少も極めて少ないことからして肝壊死の発生基盤たる限局性非可逆性鬱血が発現せず，従つて正常例に比し遮断による肝壊死が発生し難いものと思考される.